

Placental Pathology Findings in Fetuses and Neonates with Congenital Zika Virus Infection and Microcephaly

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Placental Pathology and Emerging Infections

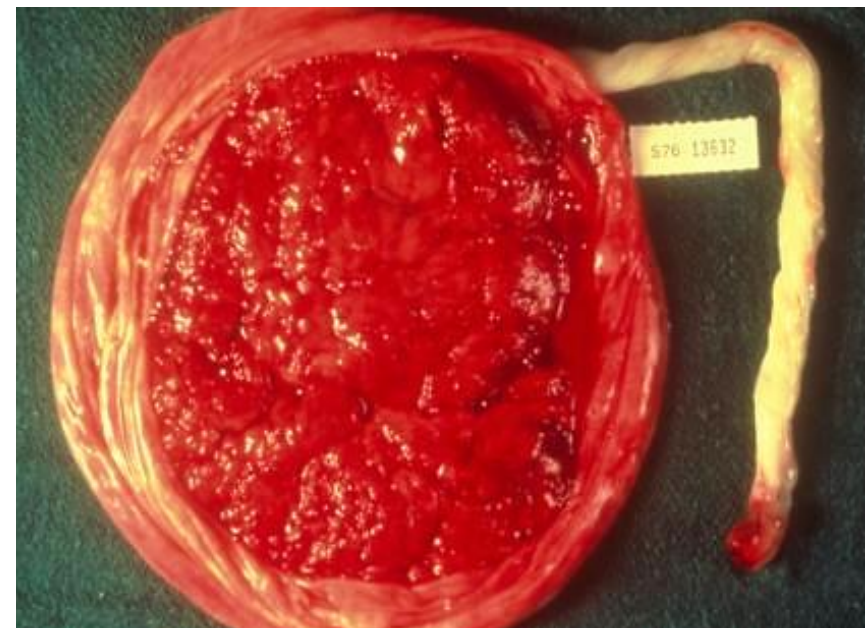
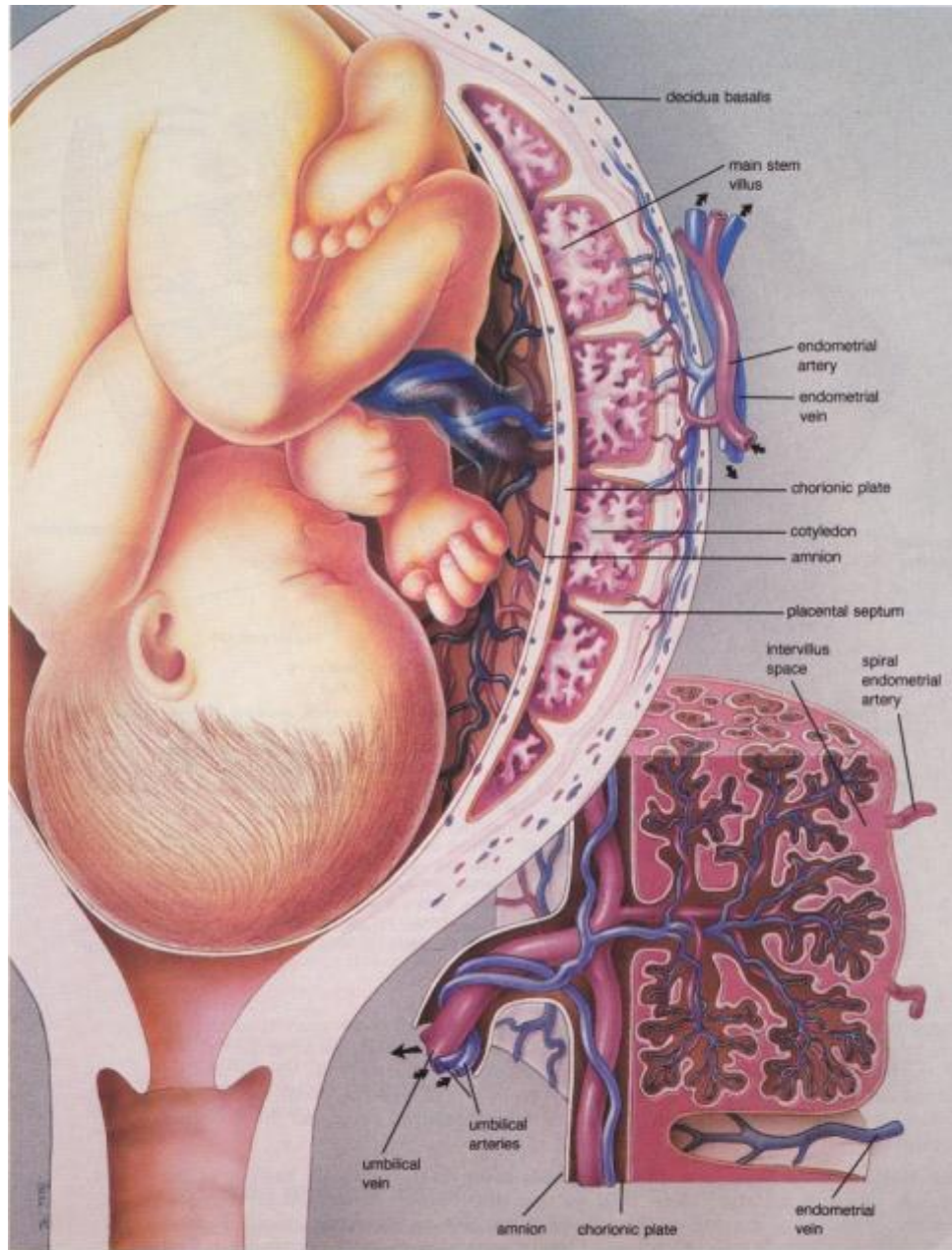
- The placenta is the largest of fetal organs, and forms a selectively-permeable barrier between the maternal and fetal circulations up to the time of birth
- Placental pathology has proven to be a sensitive & specific method for studying the vertical transmission of infectious agents between mother and fetus
- There remains little doubt that the placenta is the key organ through which fetal infection develops, and it is important that the mechanism(s) by which this process occurs be understood

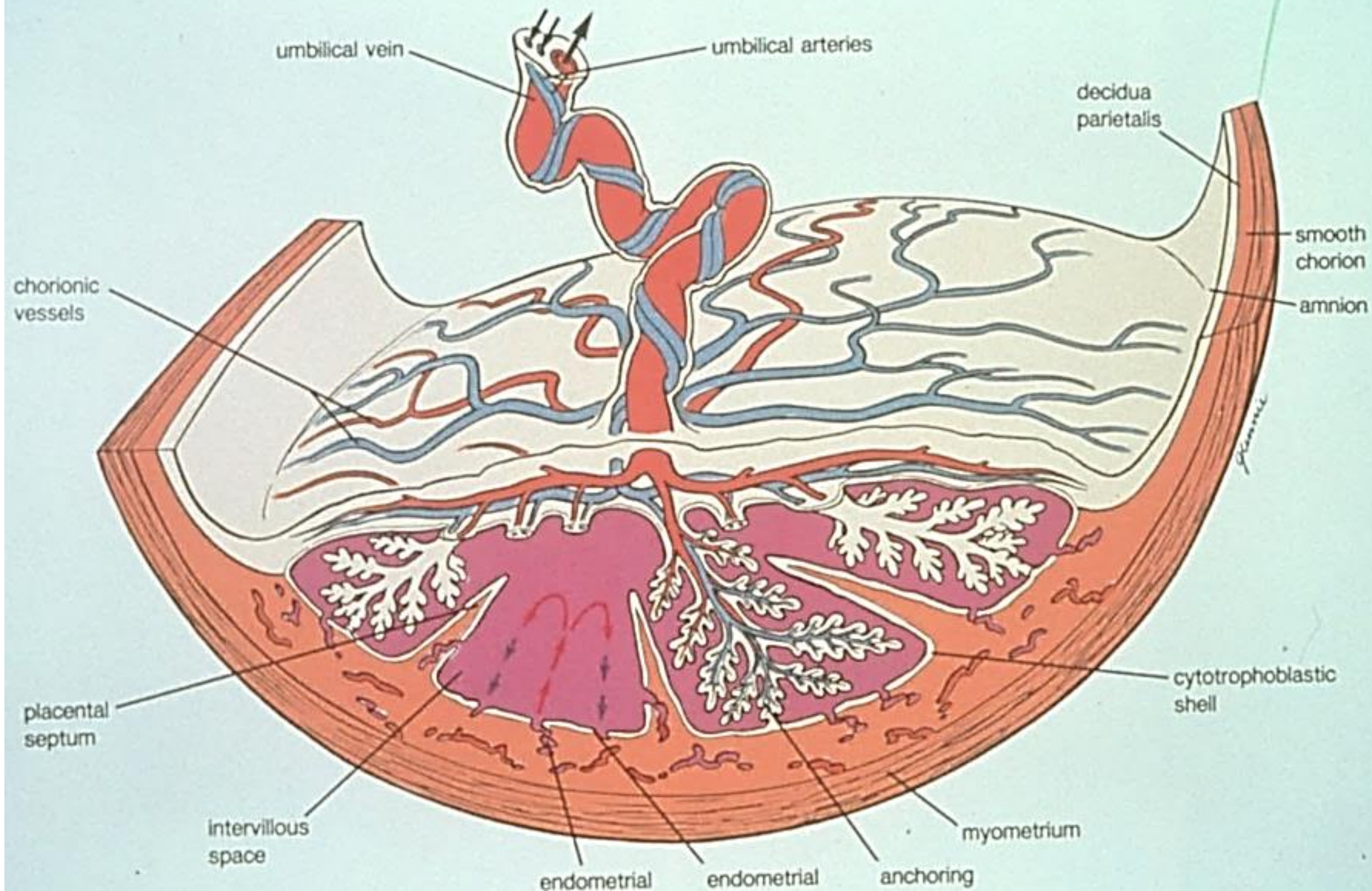
Examination of the placenta is important in the evaluation of vertical Zika virus transmission in *humans*, as well as animal models of maternal-fetal infection such as *mice* and *non-human primates*



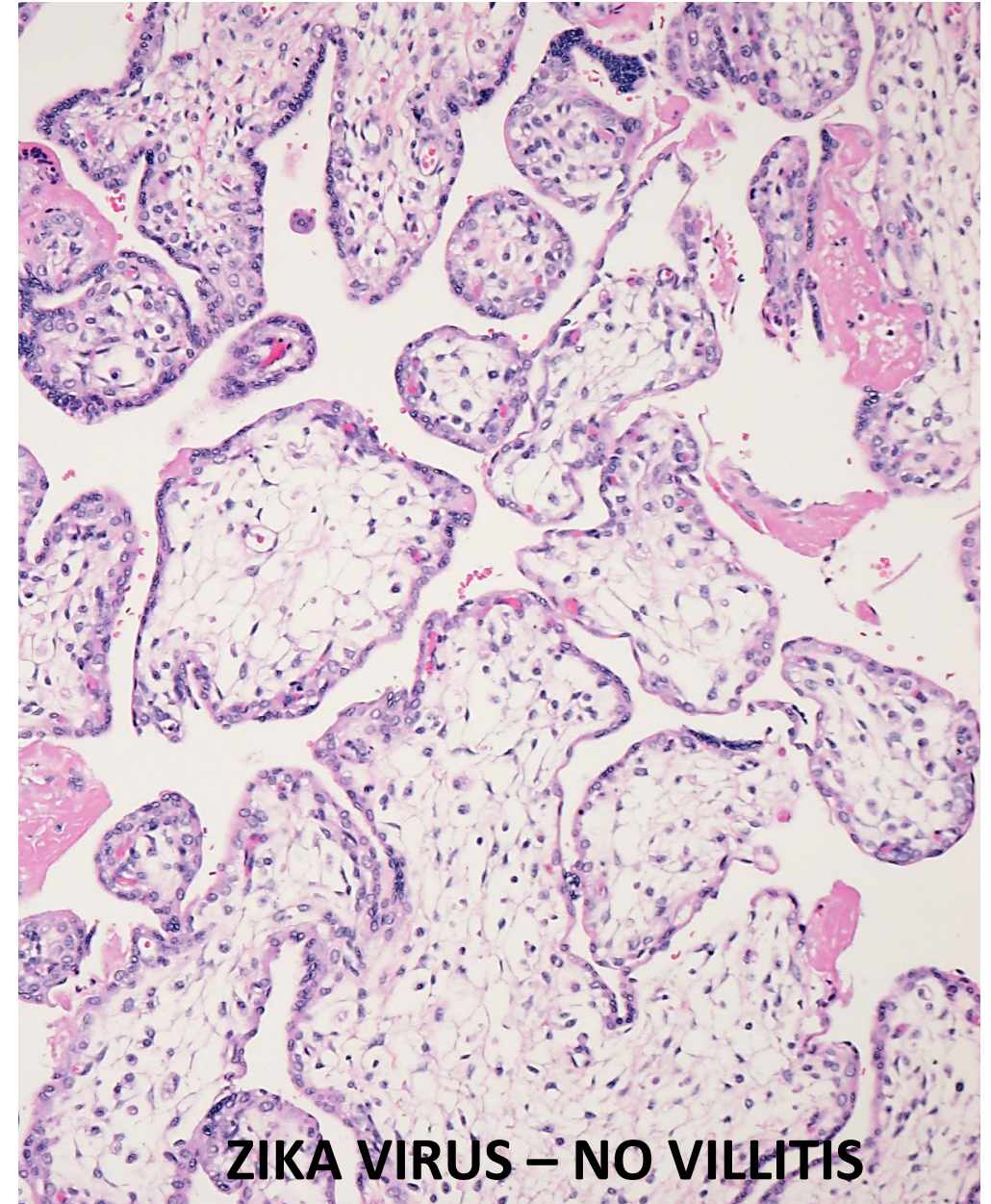
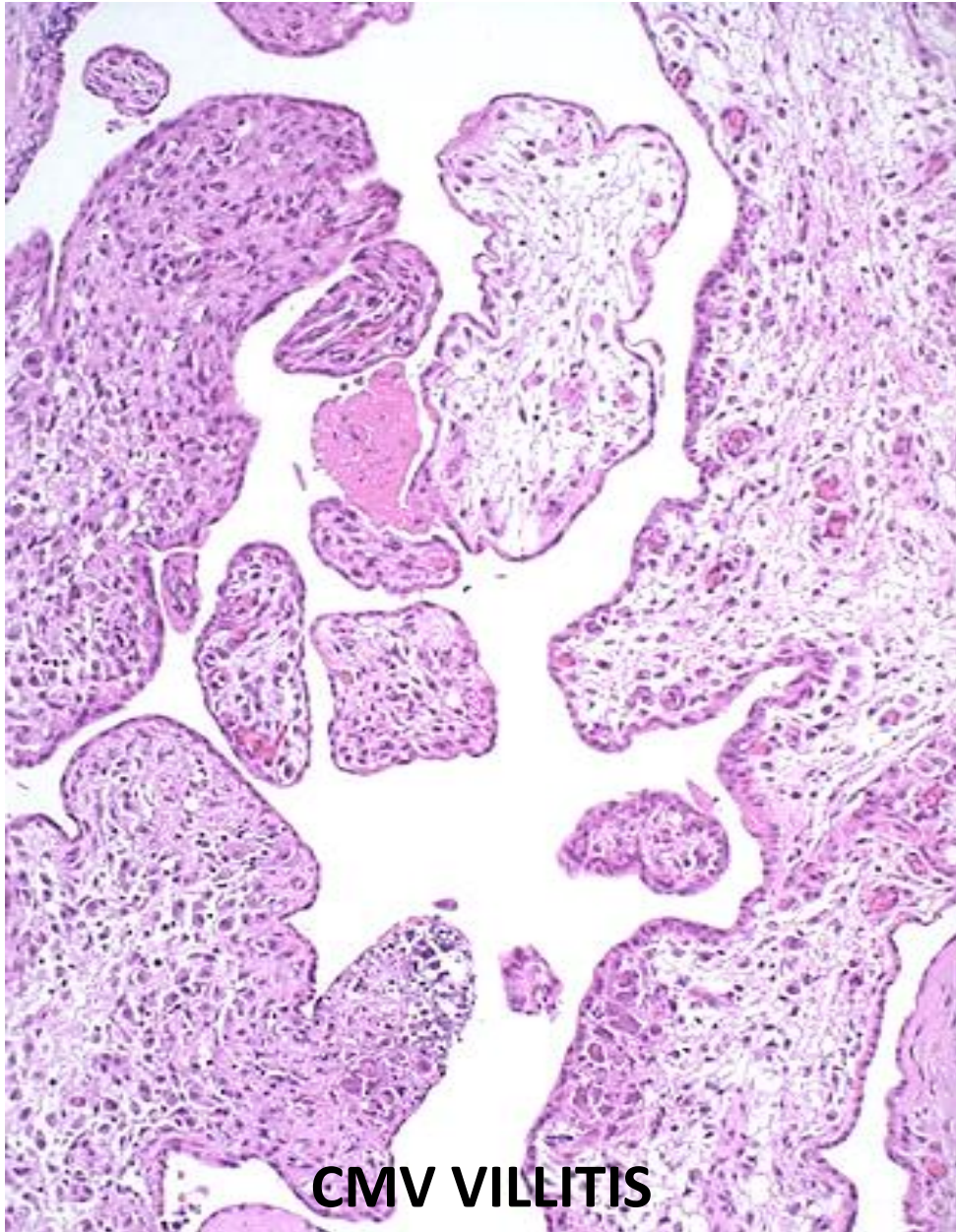
Examination of placentas from infected mothers and their fetuses can potentially reveal several important findings

- 1) the placental tissue distribution of the organism,
- 2) localization of the organism to an extracellular or intracellular environment,
- 3) the specific placental cell type(s) which the organism infects,
- 4) the relative number (load or burden) of the organisms in tissue,
- 5) the effect of the agent on the host cells and tissues,
- 6) the type of host cellular and immunological response and effect of them on the microbe, the type and
- 7) intensity of the host inflammatory response to the organism,
- 8) aspects of the reproduction of the agent in tissues,

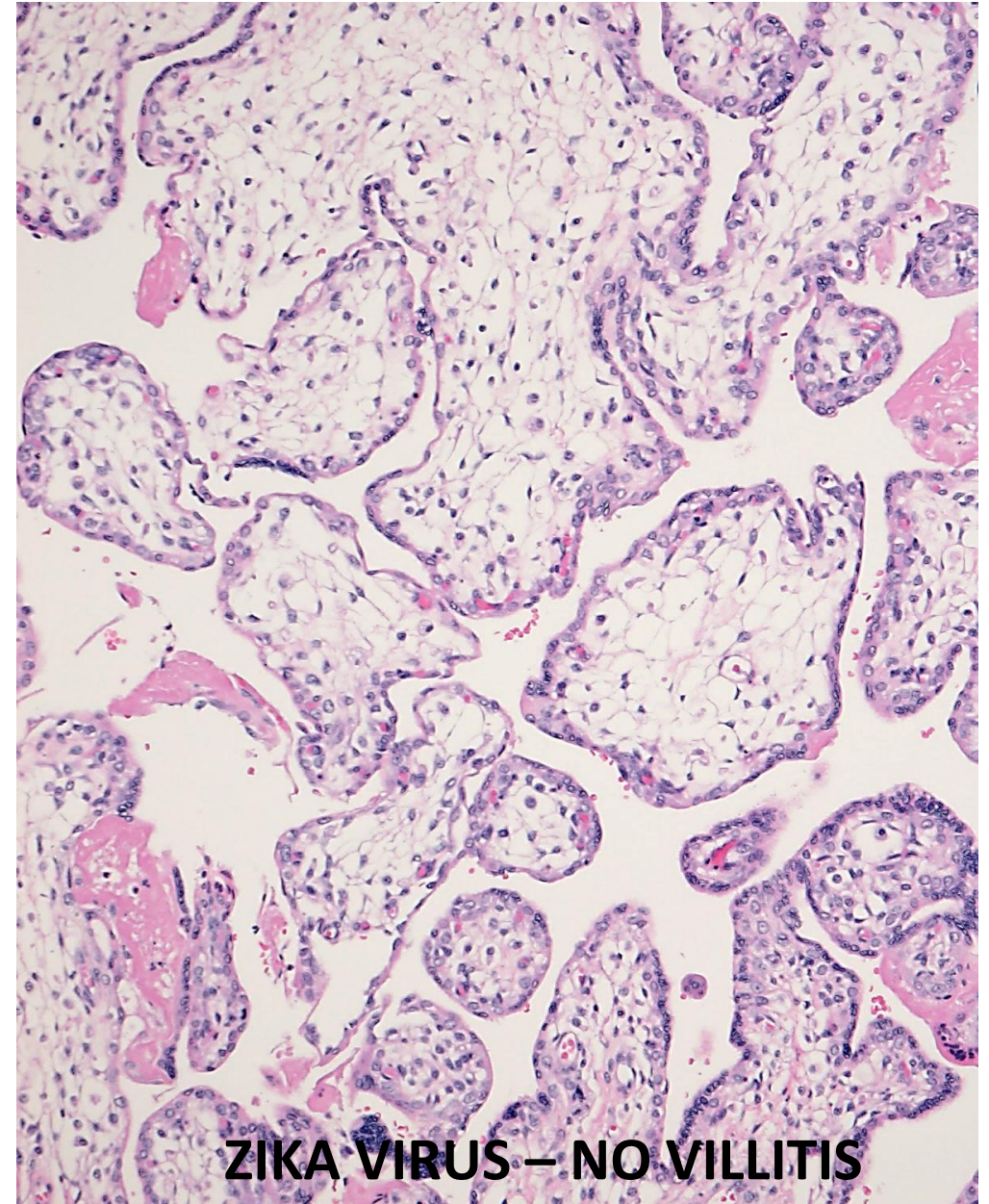
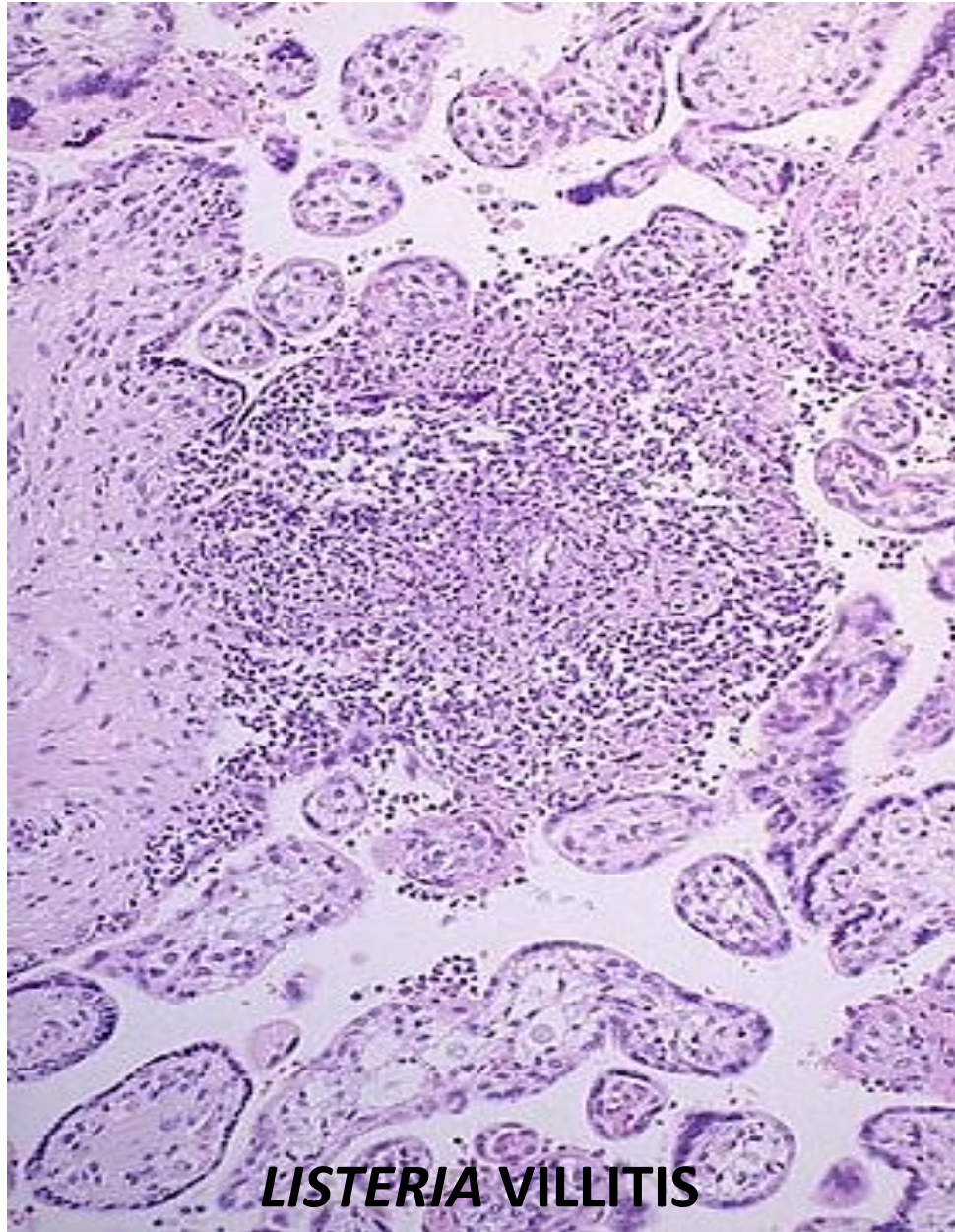




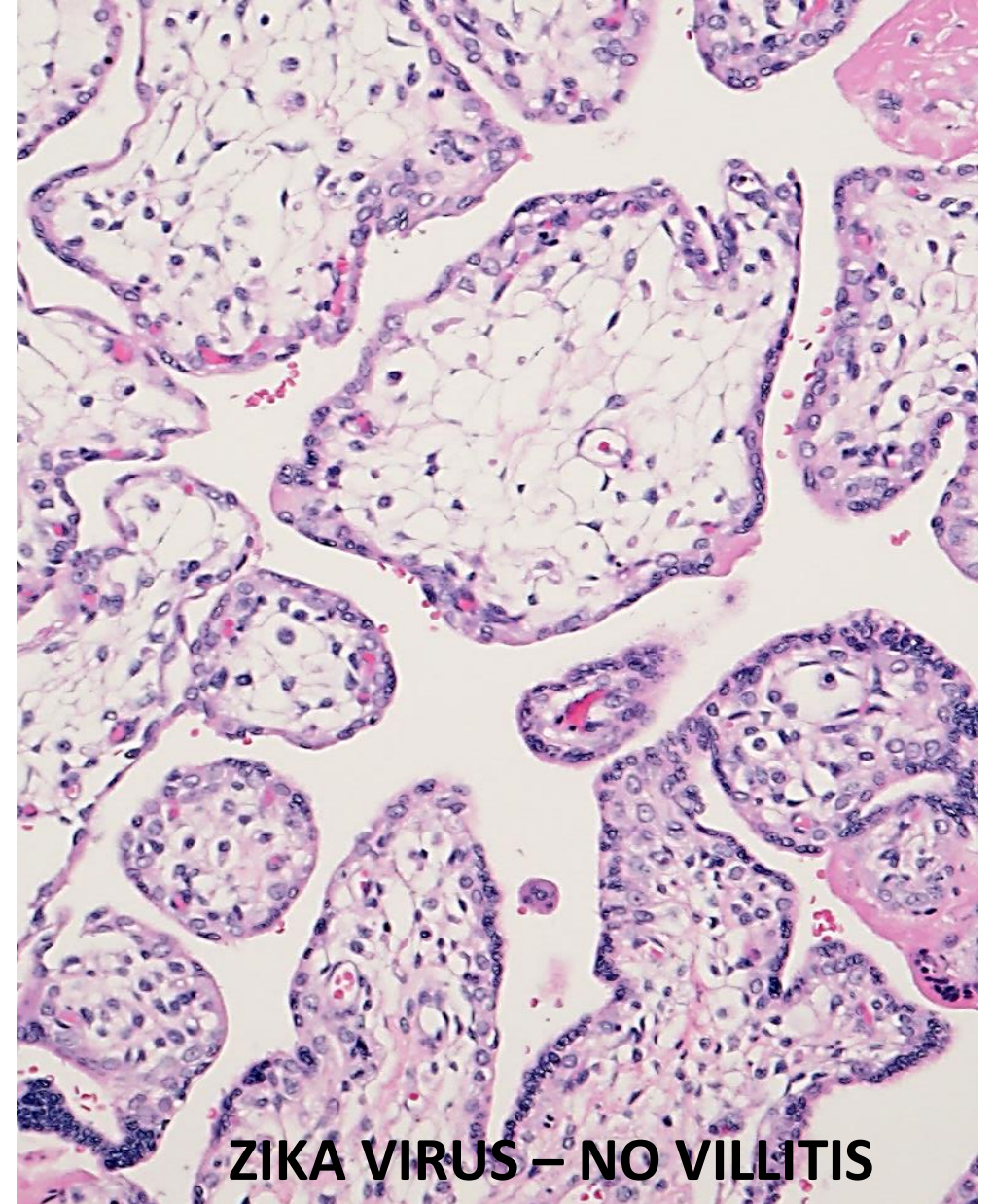
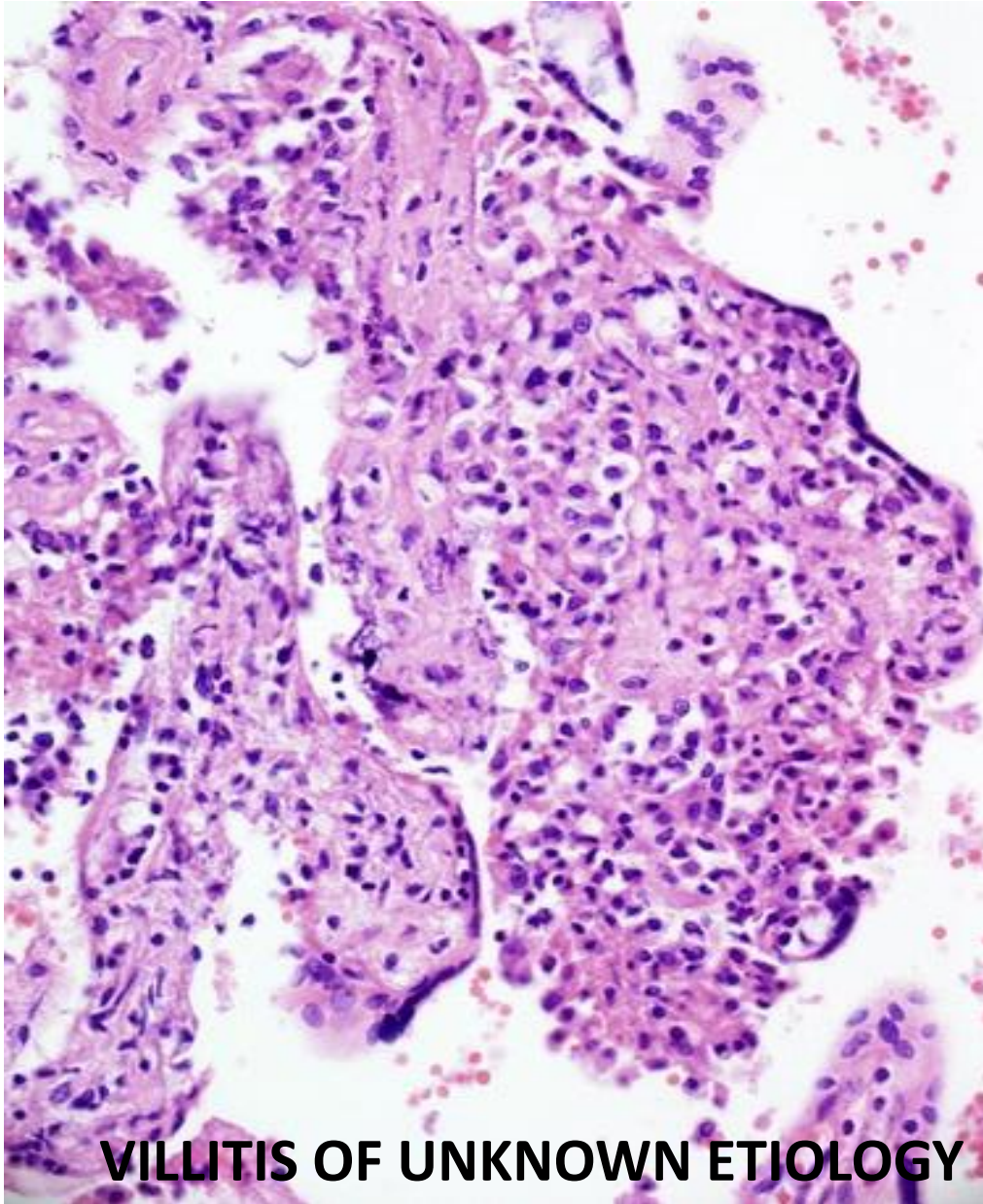
There is no appreciable inflammatory reaction to Zika virus in the human placenta



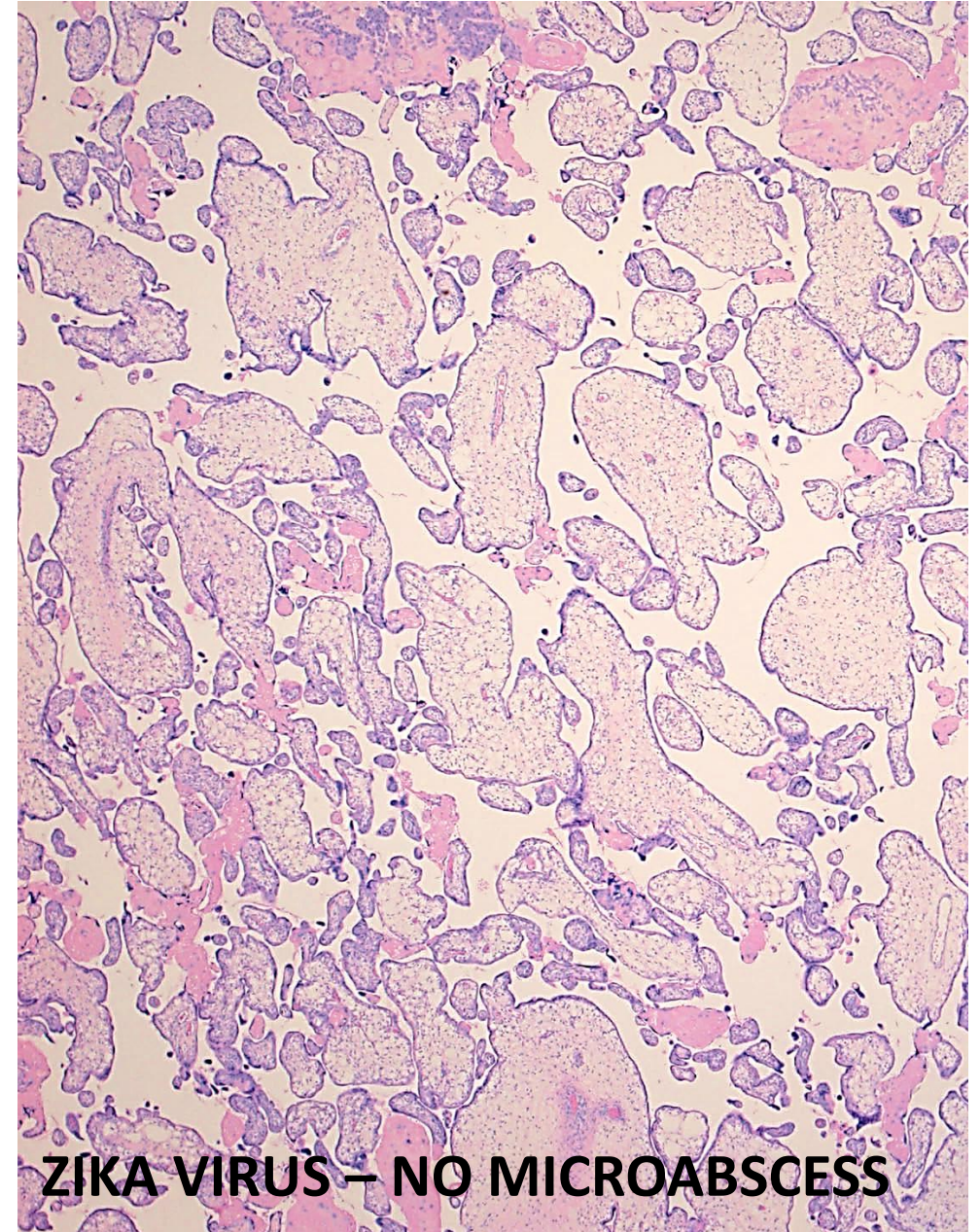
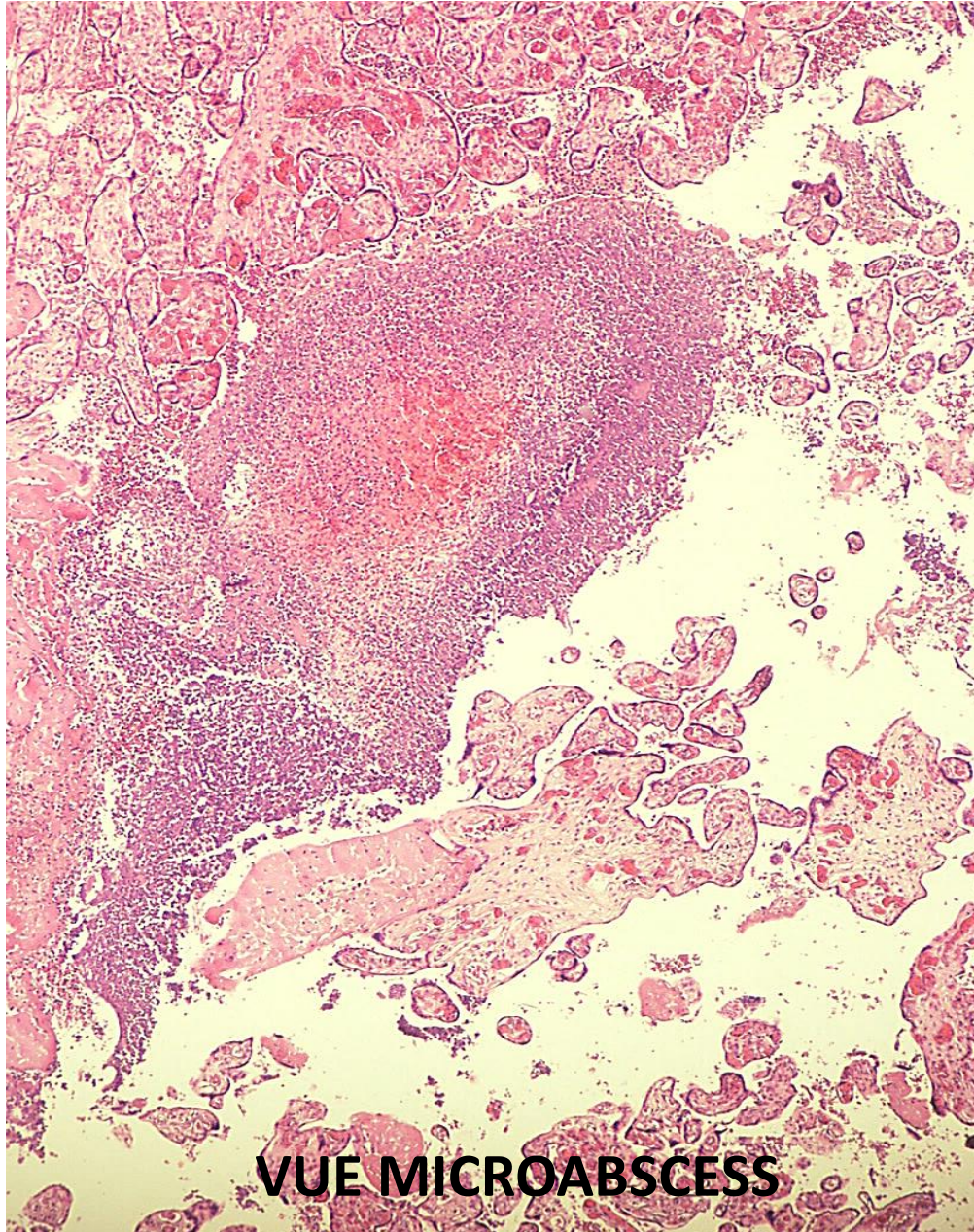
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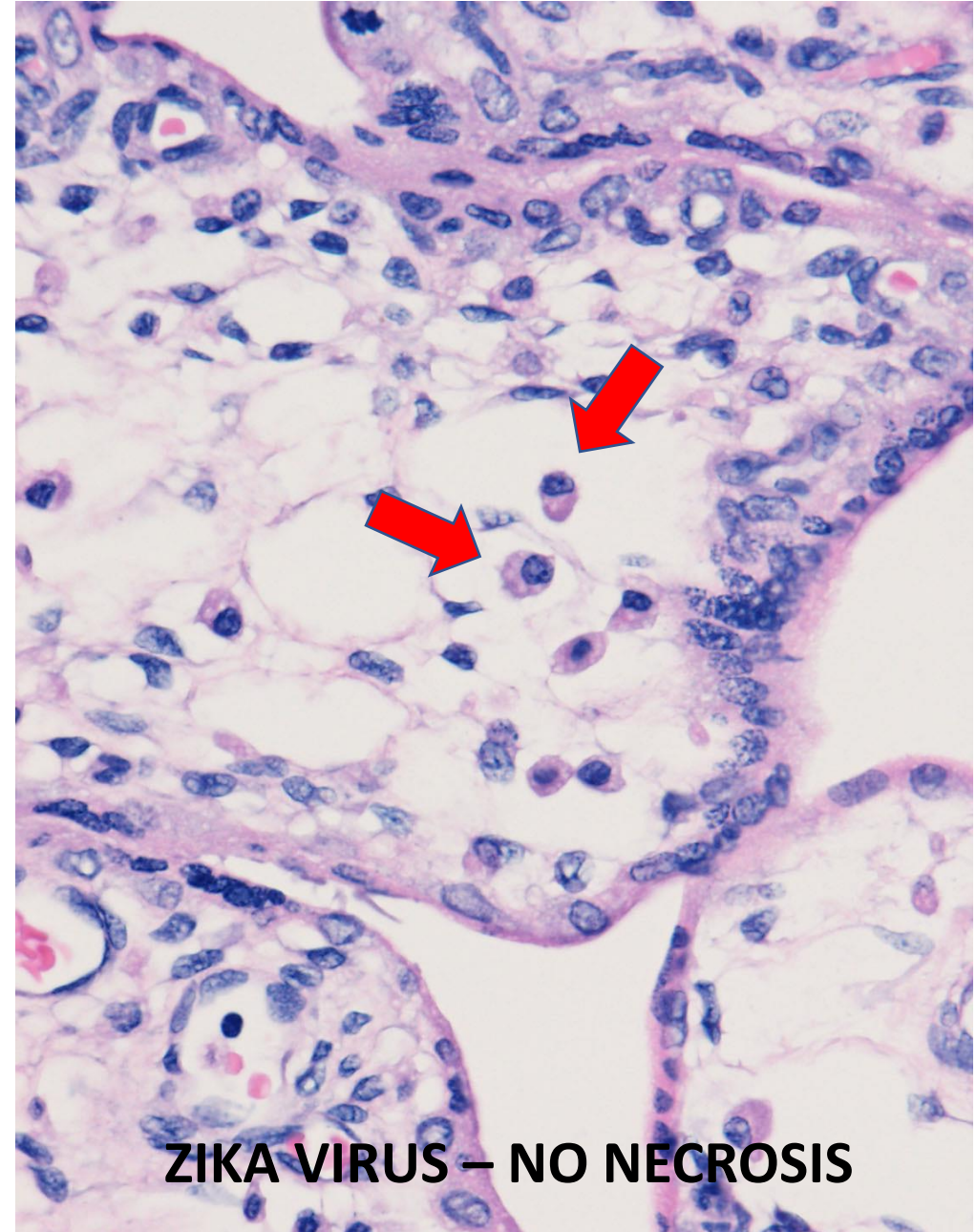
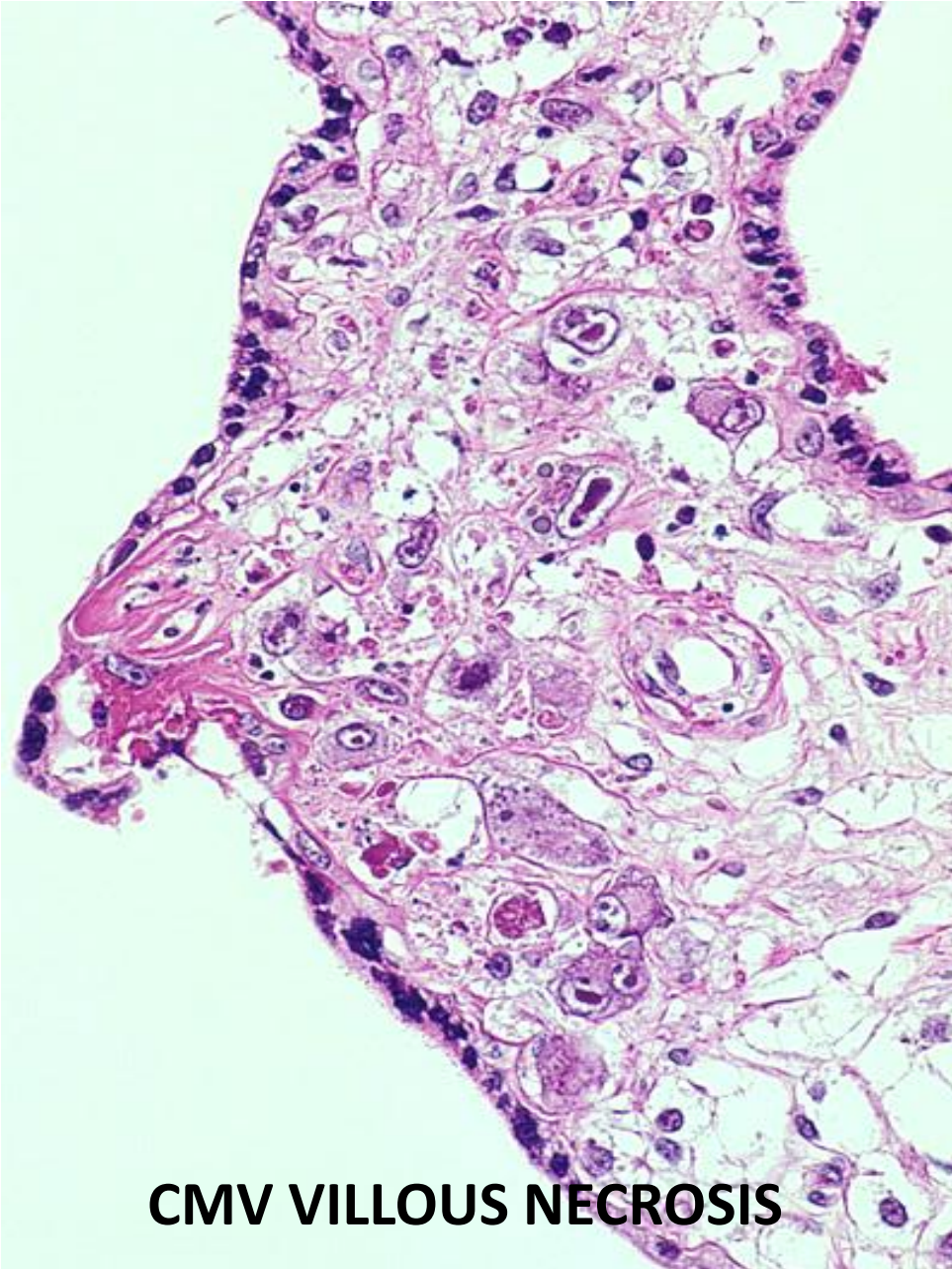
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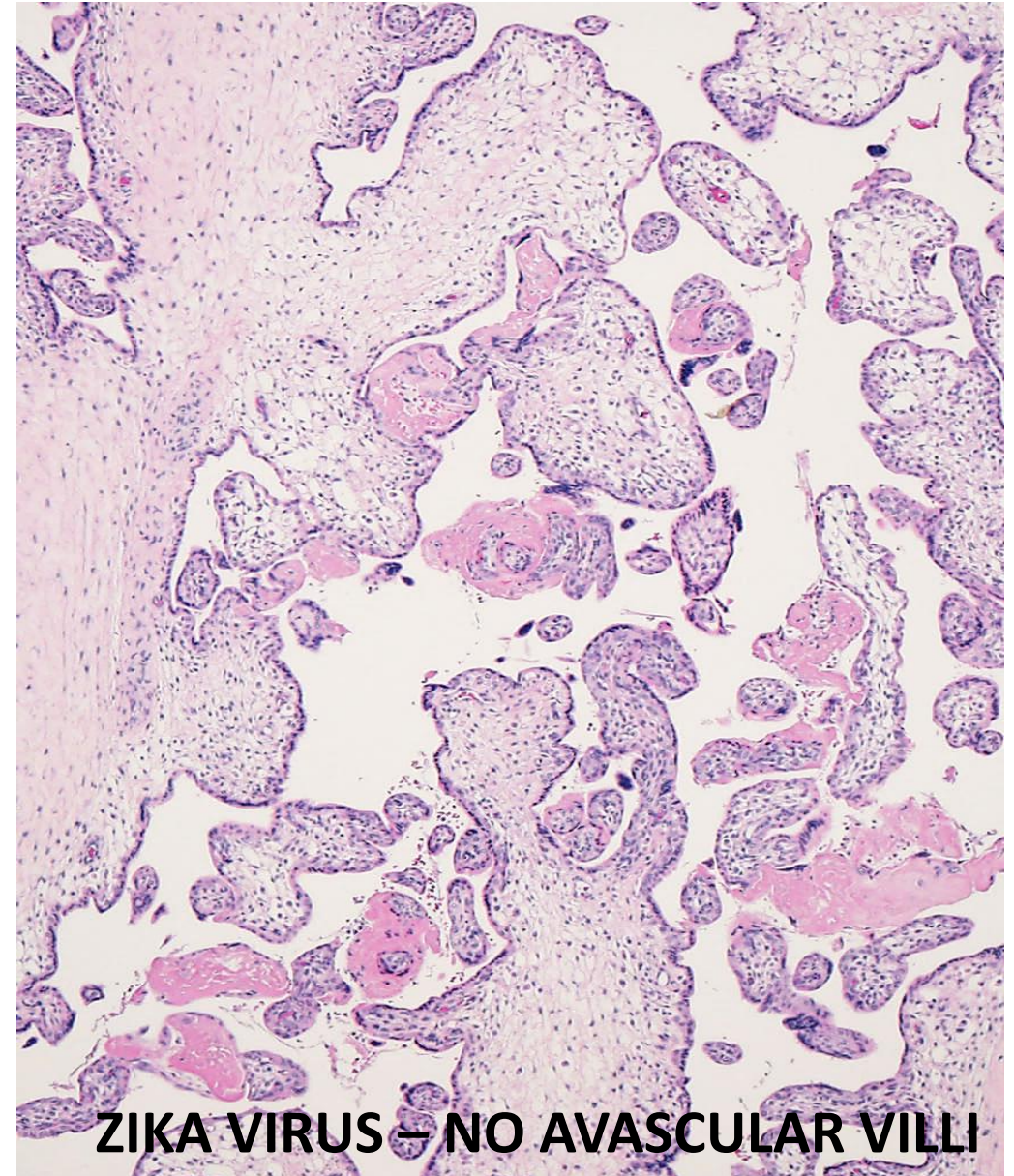
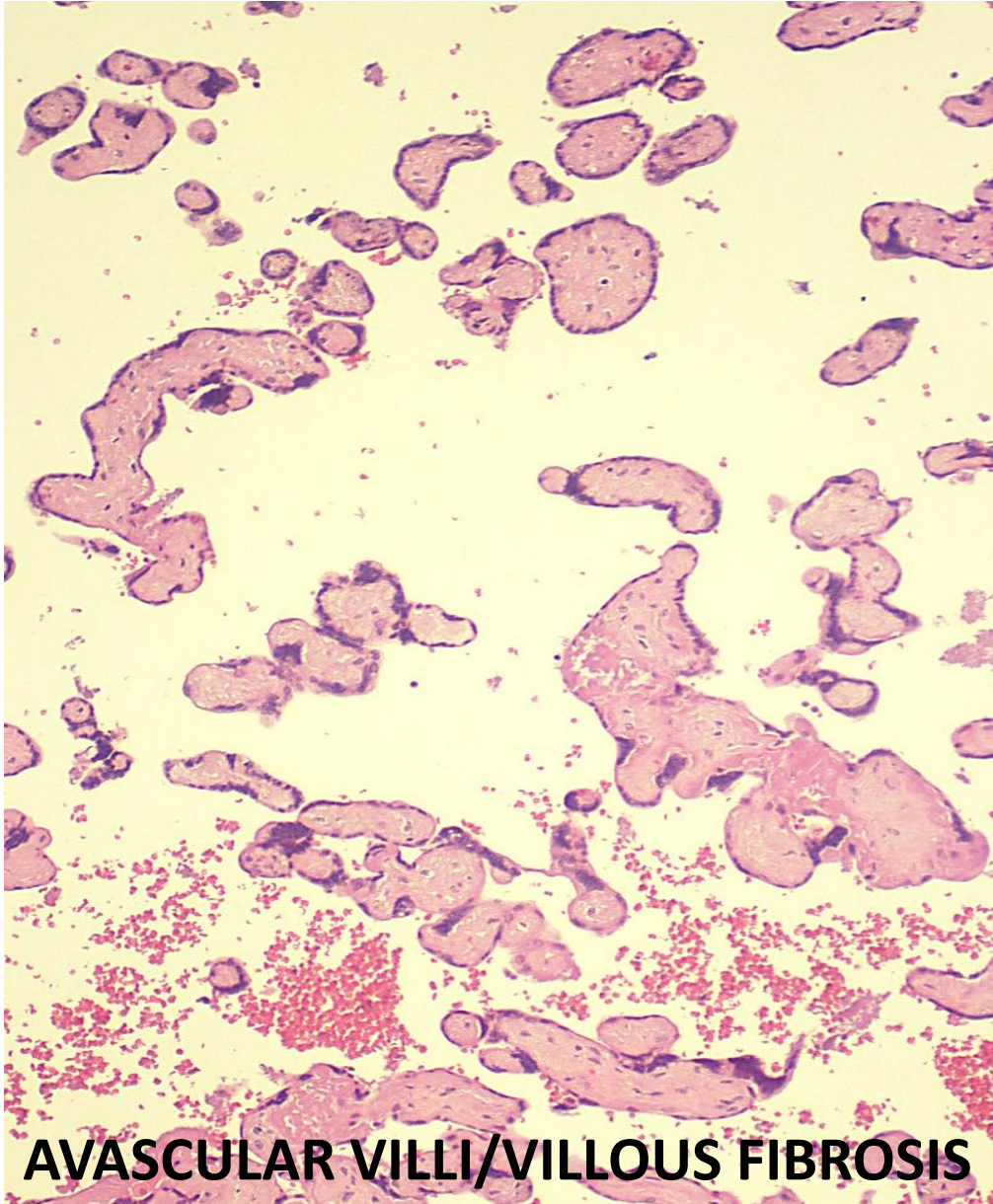
Transplacental Zika virus infection does not cause abscess formation



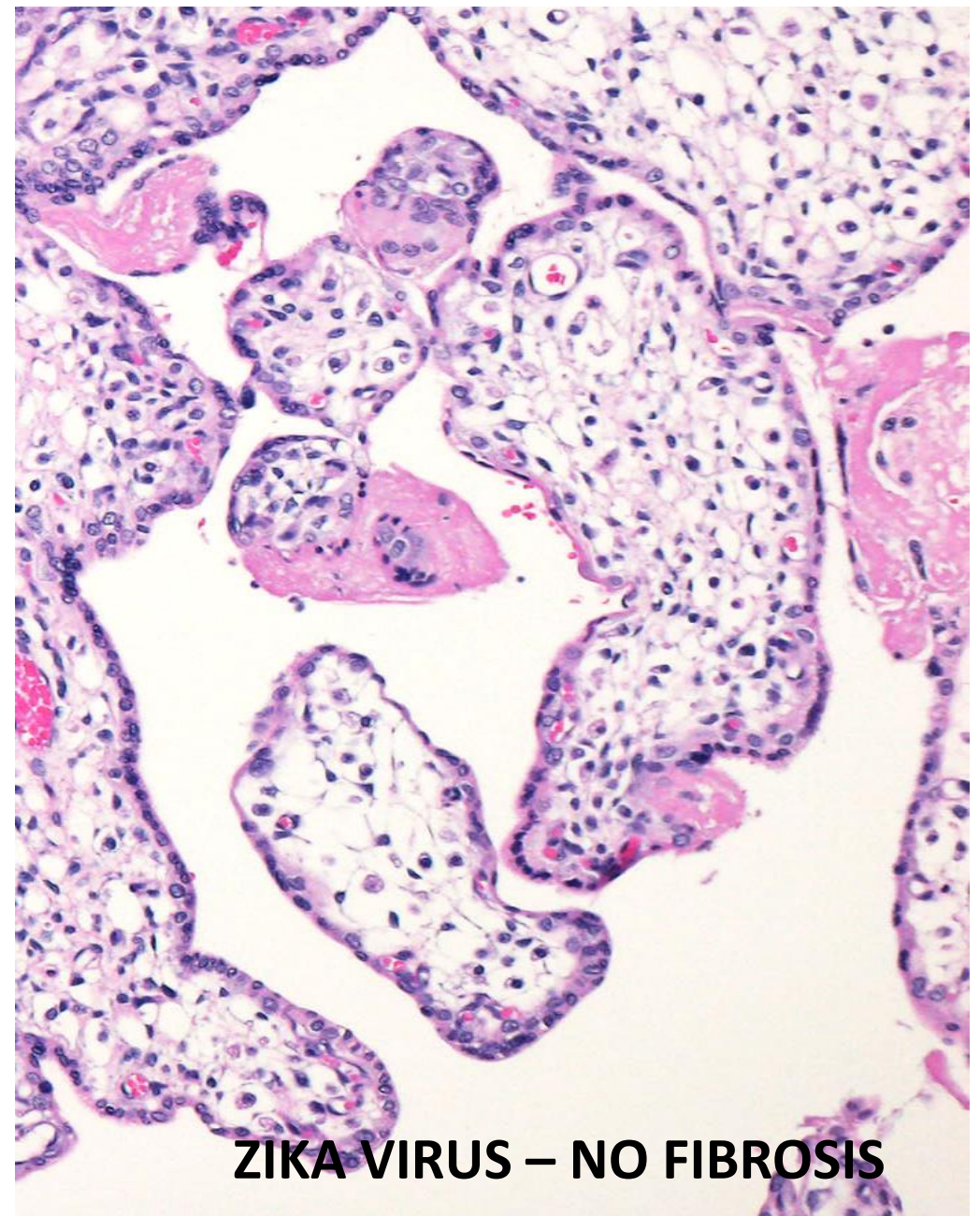
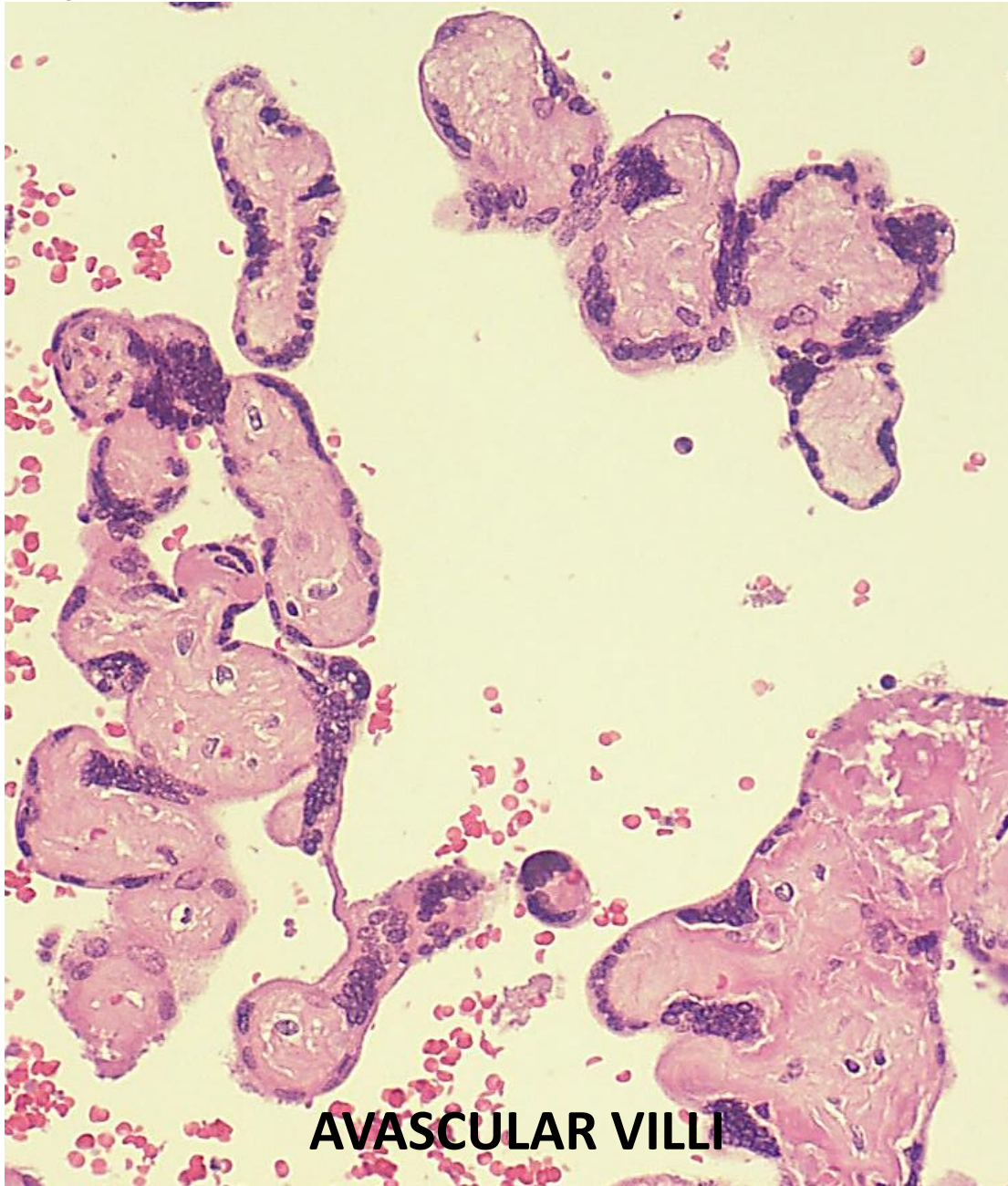
Transplacental Zika virus infection does not cause villous necrosis



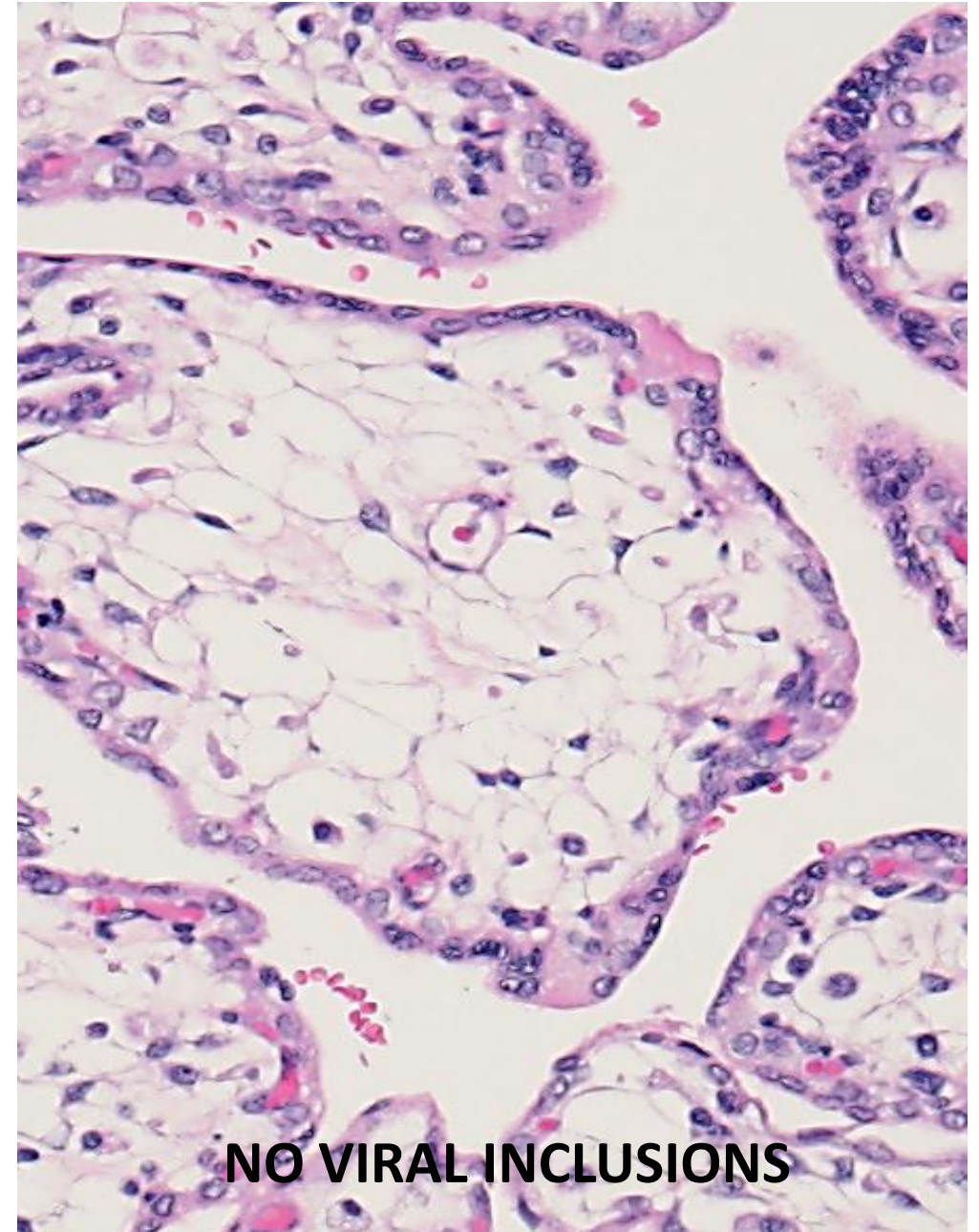
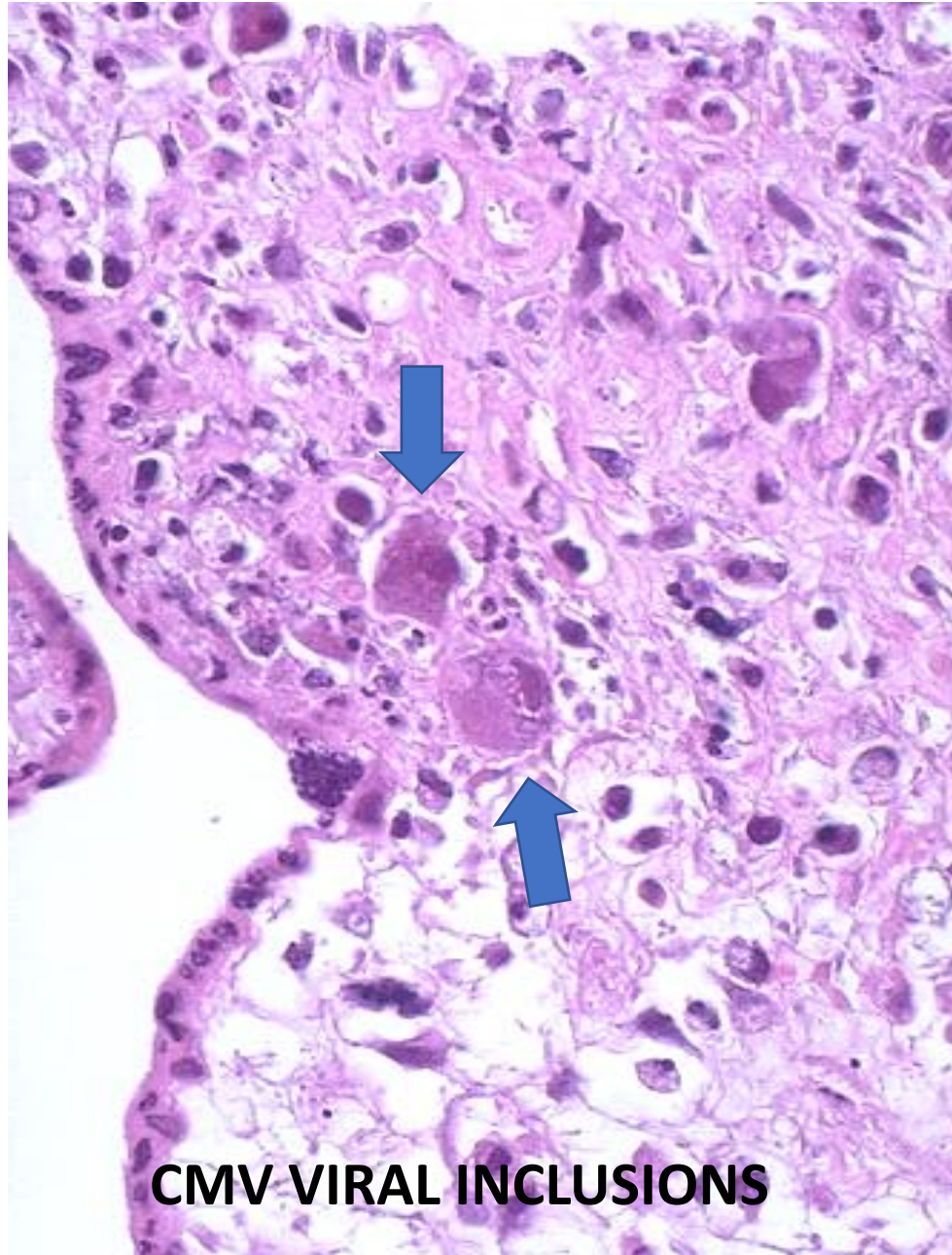
Transplacental Zika virus infection does not cause villous fibrosis (scarring)



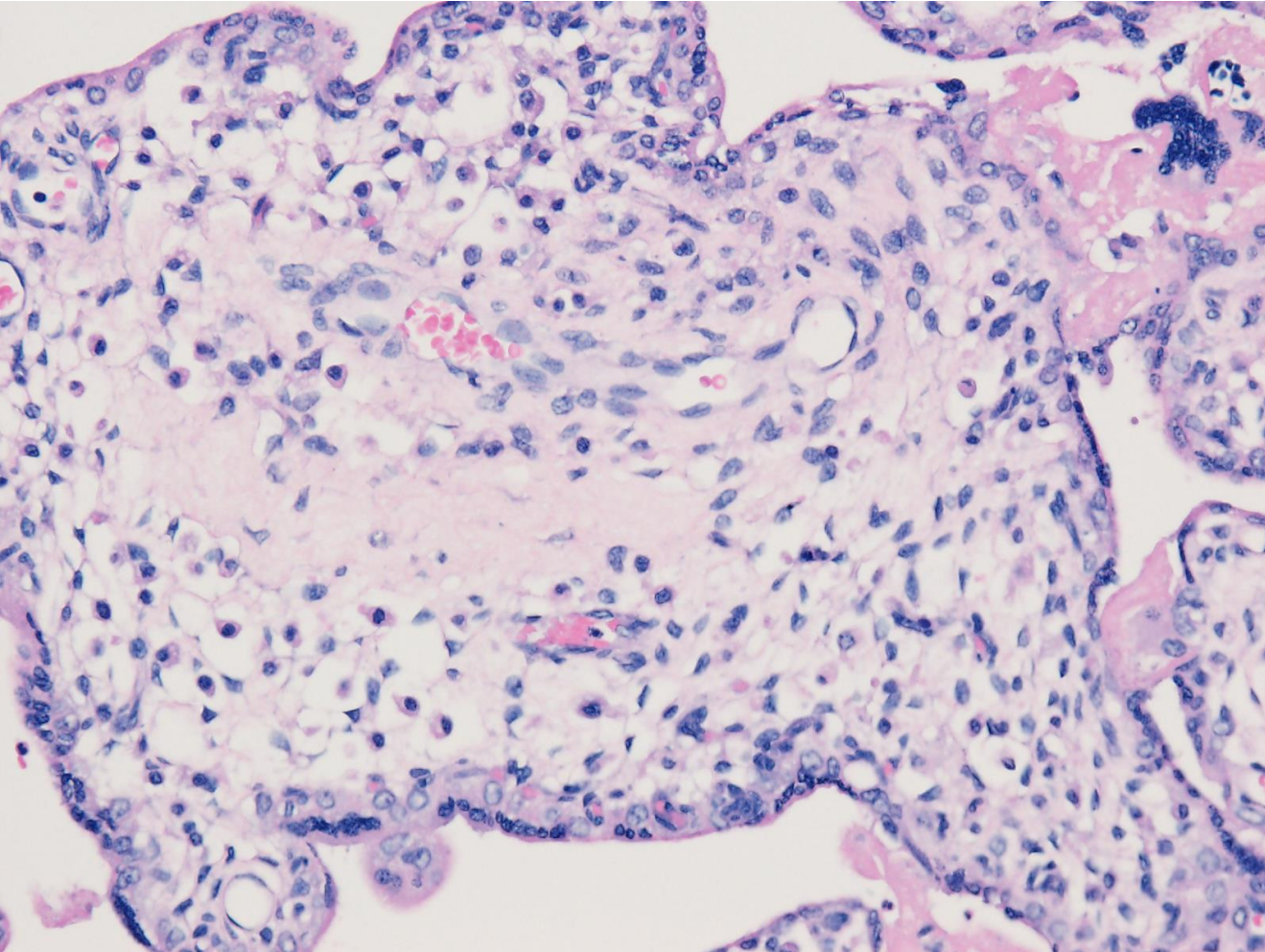
Transplacental Zika virus infection does not cause villous fibrosis (scarring)



Transplacental Zika virus infection does not cause viral inclusions



Zika Virus is Also Not Associated with:



- Placental Pathology Findings of an Ascending Infection: Acute Chorioamnionitis, Funisitis (Umbilical Vasculitis), Chorionic Vasculitis, or Deciduitis
- Maternal Inflammatory Response (MIR) in the Placenta
- Fetal Inflammatory Response (FIR) in the Placenta
- Placental Hemorrhage of Maternal or Fetal Origin
- Thrombosis or Vasculitis of Fetal Blood Vessels in the Placenta

Hofbauer Cell Proliferation and Hyperplasia Occur Following Zika Virus Placental Infection

- Hofbauer cells are fetal cells of monocytic origin and are a normal component of the stroma of the chorionic villi.
- They are believed to initially be of fetal mesenchymal origin, derived from monocyte progenitor cells of the hypoblast-derived yolk sac that have migrated to the mesenchymal core of the villi.
- As gestation progresses, it has been suggested that they are derived from a population of recruited fetal monocytes.
- Hofbauer cells are large (10 to 30 μ m diameter) cells with cytoplasmic processes which contain large vacuoles, pinocytotic vesicles, & intracytoplasmic granules.
- Their function includes phagocytosis of fluids and apoptotic materials, antigen presentation in response to infectious agents, and possibly an angiogenic role early placental vasculogenesis, maintenance of placental water balance, and an endocrine function.

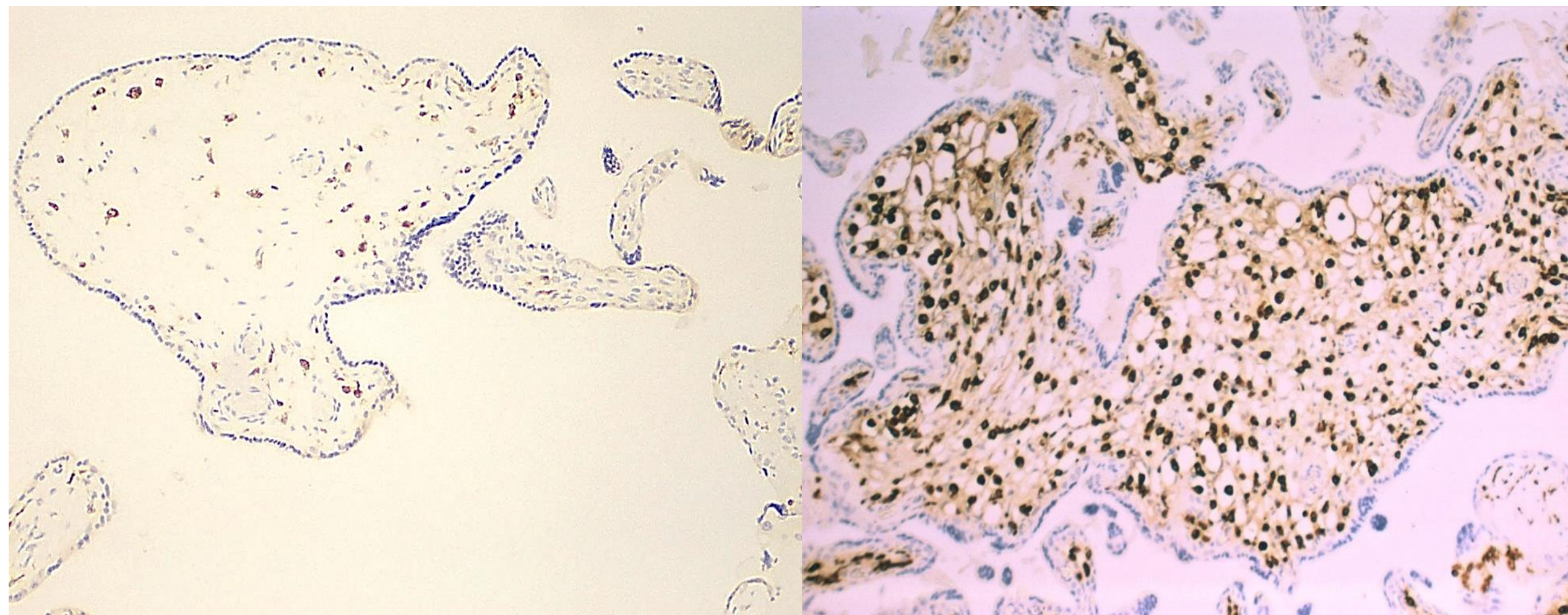
Hofbauer Cell Proliferation and Hyperplasia Occur Following Zika Virus Placental Infection

- Hofbauer cells have been characterized as M2/alternatively activated macrophages.
- In normal pregnancies, Hofbauer cells diminish in number by the 4th to 5th month of gestation, and can be difficult to identify without the use of antibody staining to macrophage antigens.
- Hyperplasia of Hofbauer cells is abnormal, and occurs in a wide variety of pathological conditions of pregnancy.
- The mechanism by which Hofbauer cell hyperplasia occurs in response to an inciting factor is, at least in part, the result of proliferation of these cells within the chorionic villous stroma.

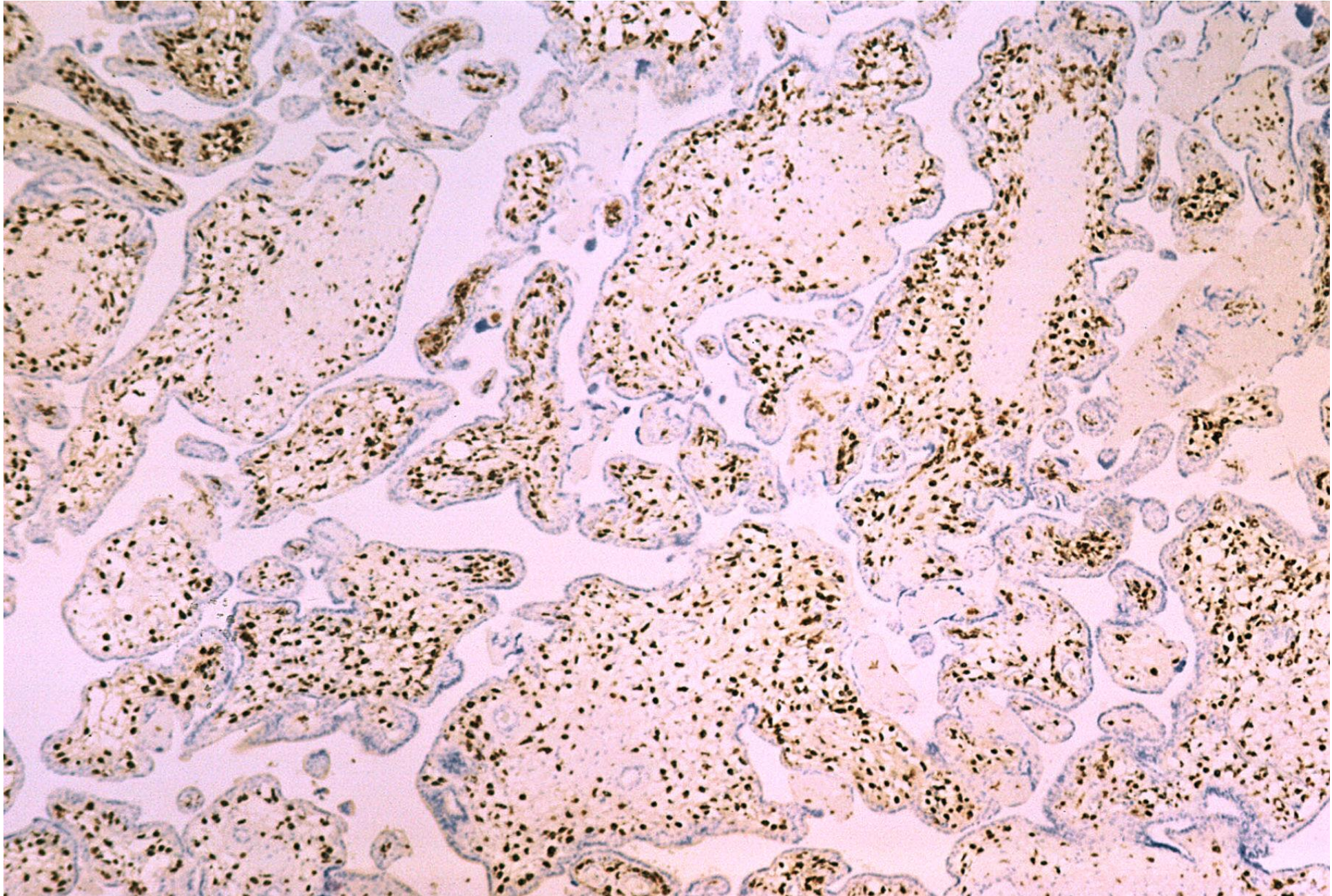
Hofbauer Cell (HC) Proliferation and Hyperplasia Occur Following Zika Virus Placental Infection

HCs in Zika virus non-infected placenta

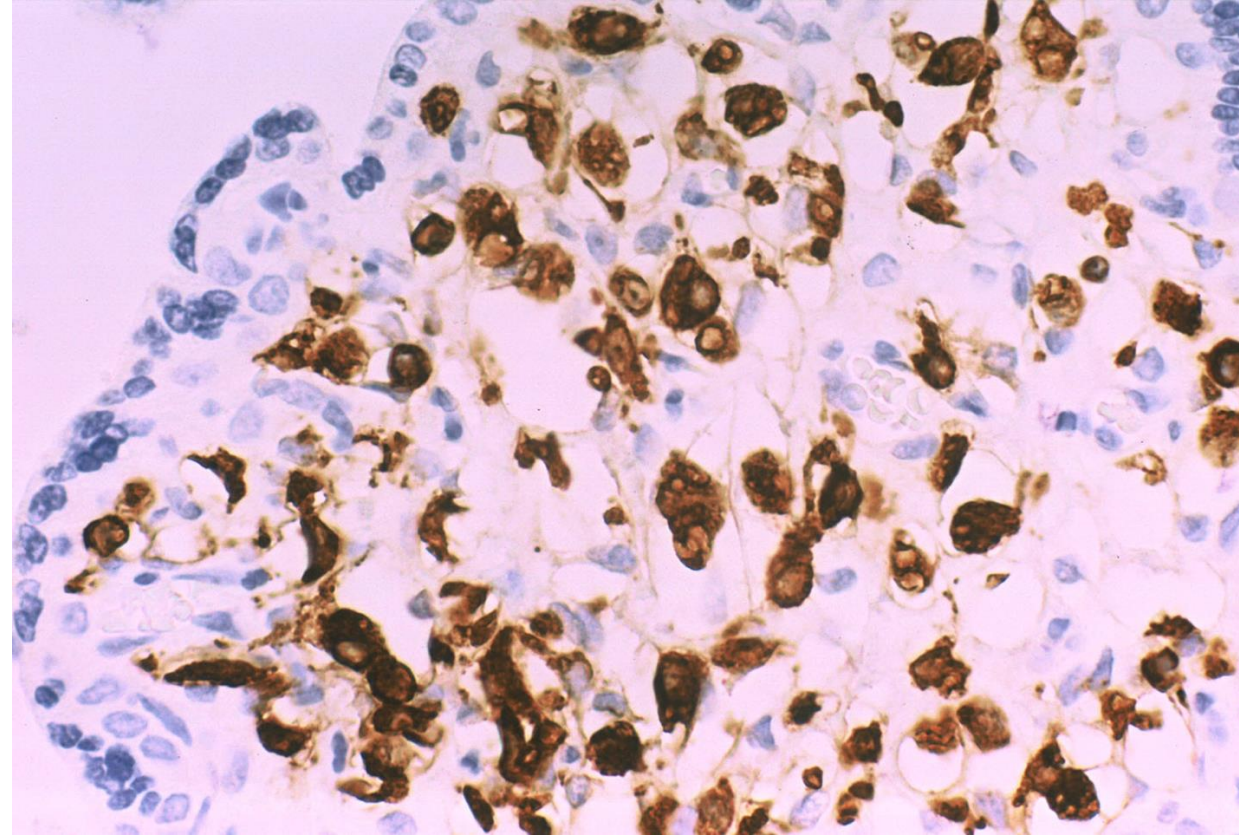
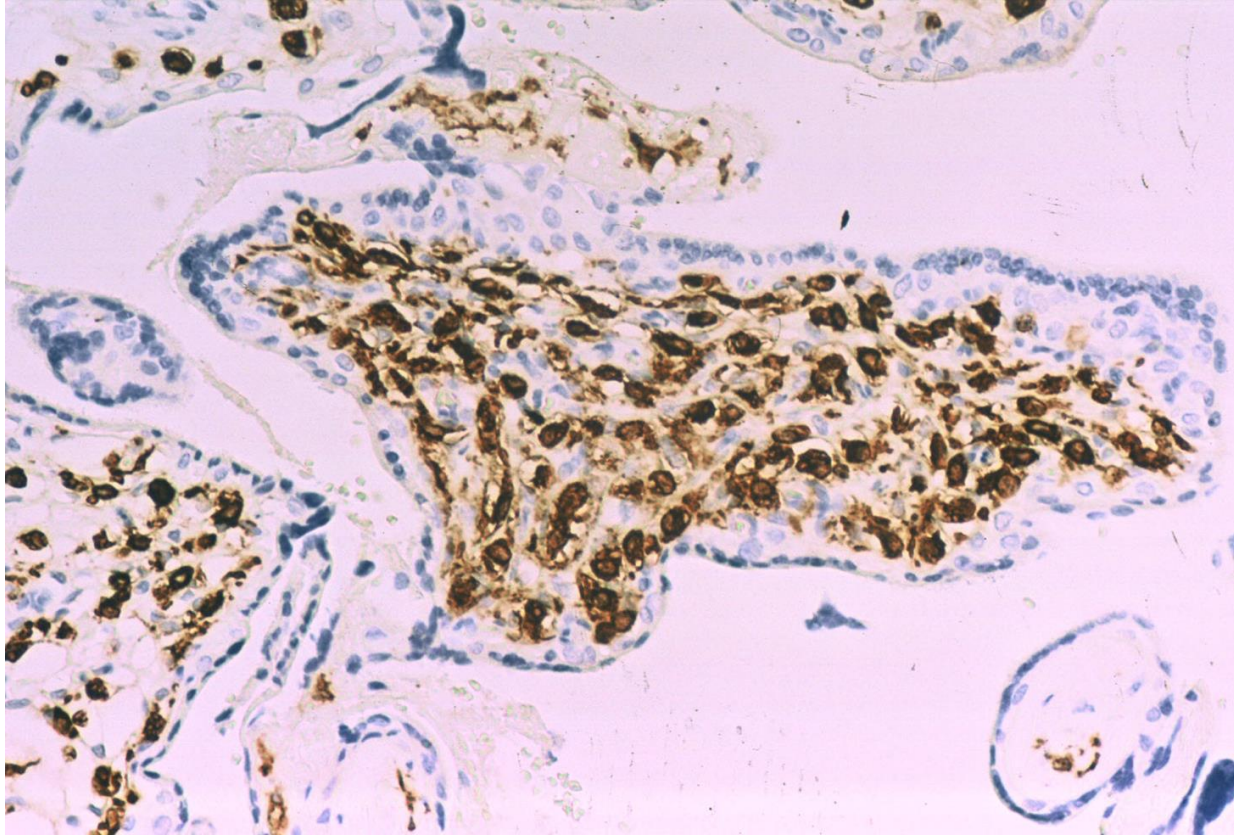
HCs in Zika virus infection and microcephaly



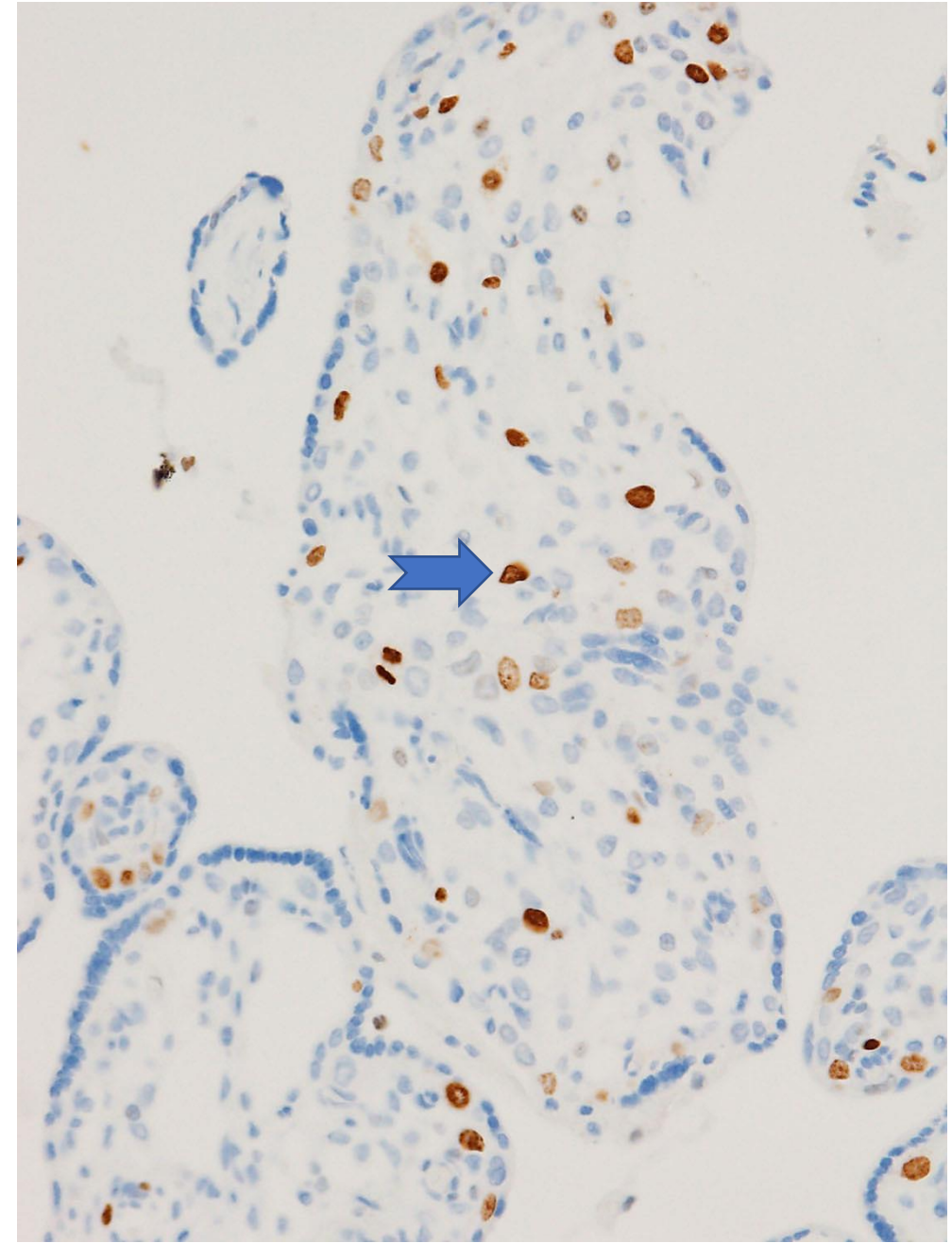
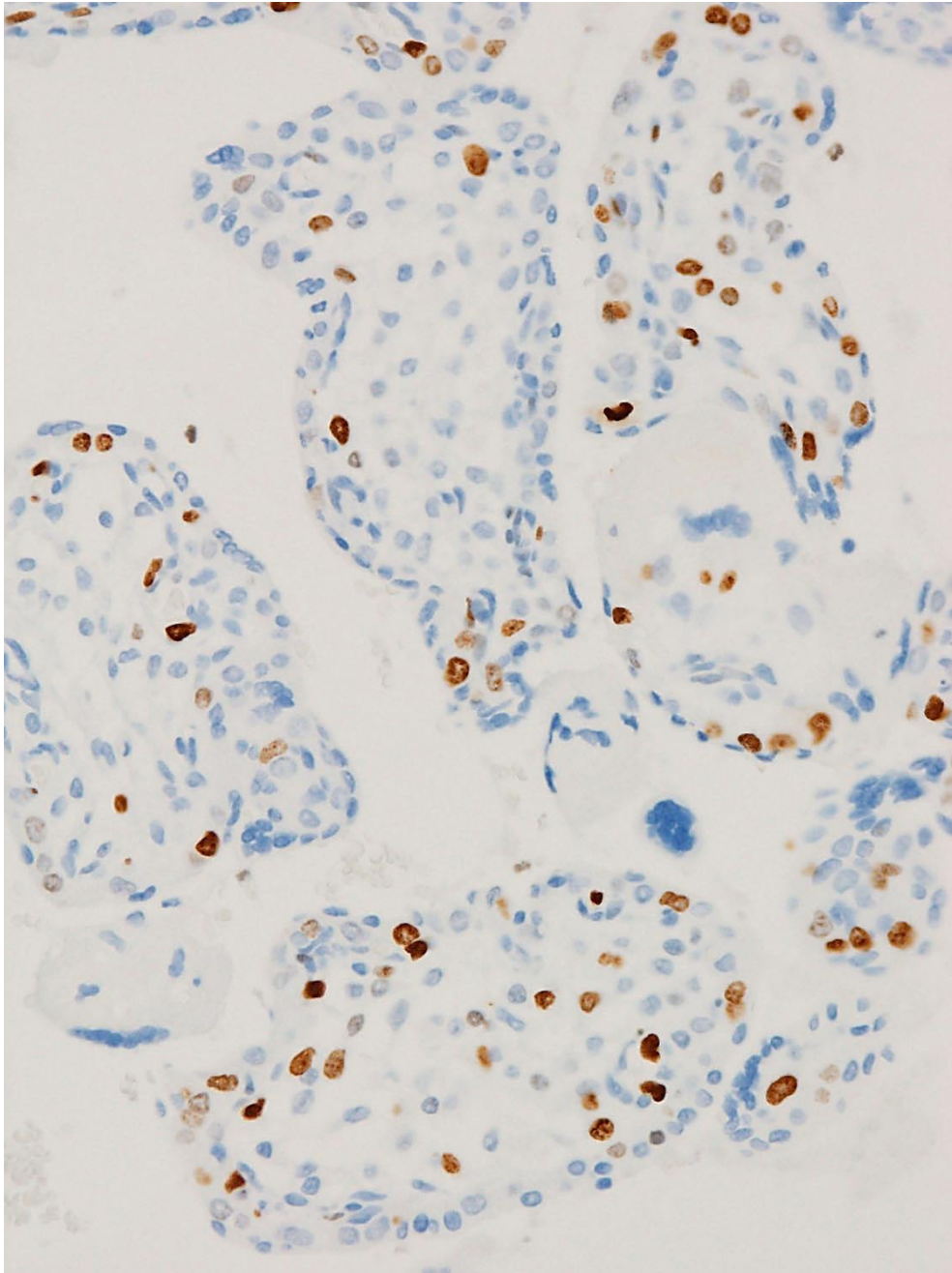
Diffuse Hofbauer Cell Hyperplasia & Zika Virus Infection



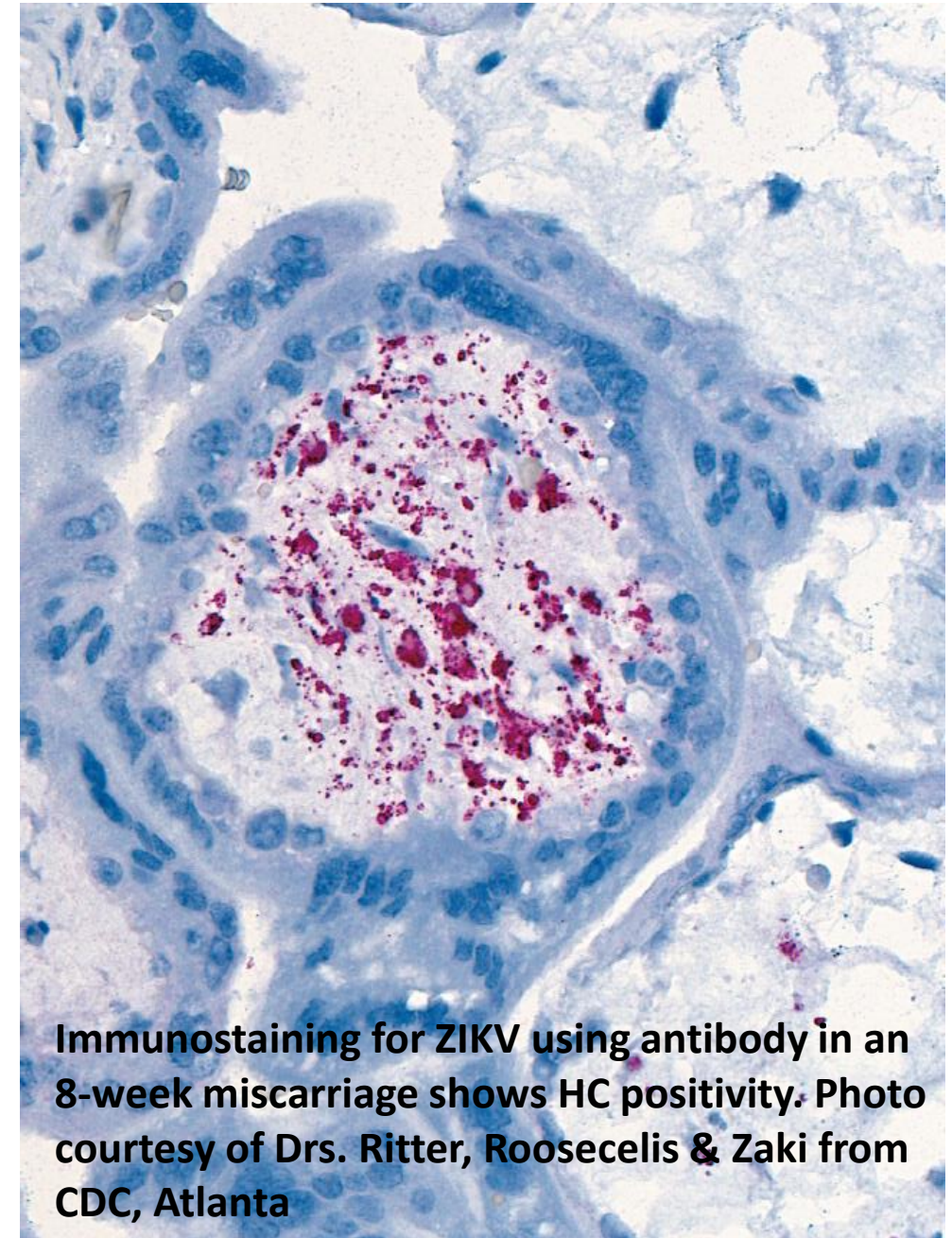
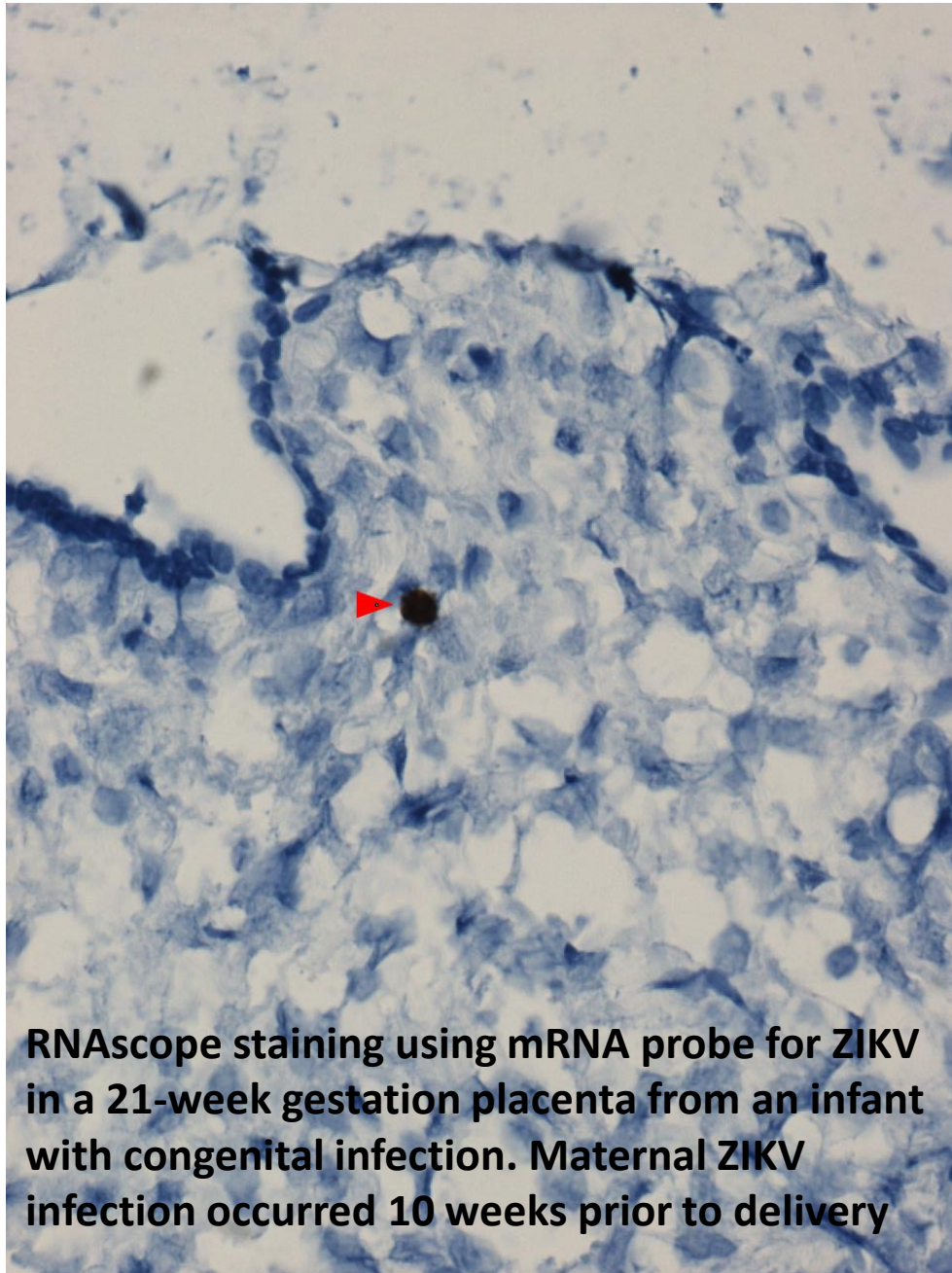
Hofbauer Cell Hyperplasia and Zika Virus Infection

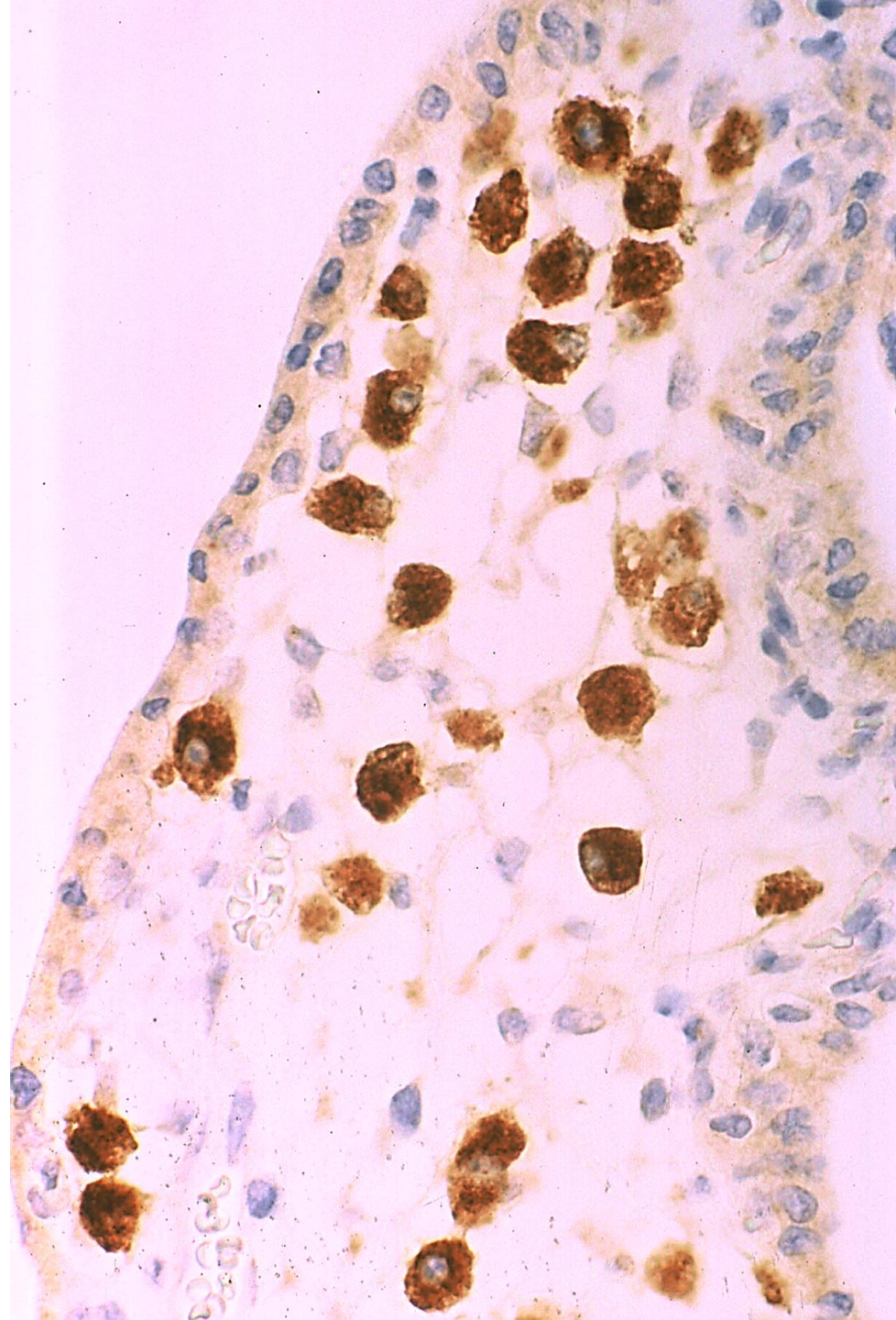


Hofbauer Cell Proliferation and Zika Virus Infection



Hofbauer Cells Are Infected With Zika Virus





- Zika virus infection of the placenta does not generally result in the production of an inflammatory response of either maternal or fetal origin
- Zika virus does not result in hemorrhage, necrosis, vascular thrombosis, or fibrosis
- The major reaction in the placenta is proliferation and hyperplasia of villous stromal macrophages, or Hofbauer cells
- Zika virus infects Hofbauer cells
- The virus can be present in HCs many weeks following the initial maternal infection
- There are differences in cellular localization of Zika virus in the placenta depending on the gestational age



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